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VIA Email

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Janice E. Chambers, PhD (Chair)
Chemical Assessment Advisory Committee Augmented for the ETBE and tBA Review
Environmental Protection Agency

RE: Notification of a Public Teleconference of the Science Advisory Board Chemical Assessment Advisory Committee Augmented for the Review of EPA's Draft Ethyl Tertiary Butyl Ether (ETBE) and tert-Butyl Alcohol (tert-butanol; tBA) Assessments [FRL-9973-47-OA]

Dear Dr. Chambers:

The American Petroleum Institute (API) is pleased to submit written comments regarding the Public Teleconference of the Science Advisory Board Chemical Assessment Advisory Committee Augmented for the Review of EPA's Draft Ethyl Tertiary Butyl Ether (ETBE) and tert-Butyl Alcohol (tert-butanol; tBA) Assessments [FRL-9973-47-OA]. API will also provide oral comment during the meeting. API is a national trade association that represents all facets of the oil and natural gas industry, with 625 plus members that include large integrated companies, as well as exploration and production, refining, marketing, pipeline and marine businesses, and service and supply firms. As a core component of our business model, we prioritize the promotion of public health and environmental safety while ensuring a strong, viable and sustainable U.S. oil and natural gas economy. Many API members are impacted by IRIS assessments. API advocates for risk assessment processes that use the best available science, are transparent, and provide opportunities for public engagement.

API's comments are summarized below and are subsequently explained in detail. These comments recapture and elaborate upon oral and written comments that API provided at a February 1-2, 2018 workshop at the National Research Council (NRC) of the National Academies of Science, Engineering, and Medicine entitled "Review of Advances Made to the IRIS Process".

1) **The lack of expert judgement in the ETBE and tBA assessments is inconsistent with responsible scientific practice, NRC recommendations and EPA policy. This is a substantive scientific concern because expert judgement in pathology is necessary to determine the human relevance of the non-cancer endpoints selected by EPA for both risk assessments.**
2) **Derivations of toxicity values for cancer endpoints for ETBE and tBA were inconsistent with NRC recommendations, EPA guidelines, and the statements of**

other EPA offices. This is a substantive scientific concern because the low dose linear extrapolations applied could result in risks of concern at levels orders of magnitude lower than a threshold (reference dose, aka RfD) approach.

3) **The numerical value for the oral slope factor for ETBE differs in the Public and Peer Review drafts for ETBE but no rationale was provided for this difference. This is not transparent. This is a substantive scientific concern because this value drives the oral cancer risk assessment for this chemical and because the NRC has voiced concerns about transparency in IRIS assessments.**
4) **The inconsistencies with responsible scientific practice, NRC recommendations, EPA policy, the decisions of other EPA offices, and the lack of transparency noted above have substantively impacted both assessments. These indicate that recent improvements in the IRIS *process* have yet to result in improved risk assessment *products.* The ETBE and tBA assessments should be revised to address these substantive scientific concerns.**

DETAILED EXPLANATION OF COMMENTS

1) **The lack of expert judgement in the ETBE and tBA assessments is inconsistent with responsible scientific practice, NRC recommendations and EPA science policy. This is a substantive scientific concern because expert judgement in pathology is necessary to determine the human relevance of the non-cancer endpoints selected by EPA for both risk assessments.**

- ***Lack of expert judgement is inconsistent with responsible scientific practice***

Expert judgement in pathology requires, among other things, subject matter expertise sufficient to evaluate pathological data in *in-life* research studies and pathology working group reports, both of which are generally performed by expert pathologists. Subject matter expertise in (veterinary) pathology is refined to such an extent that training and board certification beyond MD, DVM, and graduate degrees are evident amongst professional pathologists.

Generally speaking, the decision to use data related to pathological effects in animals for human risk assessment is arguably a decision for which responsible scientific practice would indicate that expert judgement in pathology should be applied. This point is even more salient in the specific cases of ETBE and tBA, which require expert-level ability to distinguish between non-human relevant pathological effects due to chronic progressive nephropathy (CPN) or α_{2u}-microglobulin and any human-relevant pathological effects that may be attributable to the test substance.

The listed credentials and biographies of the authors, contributors, reviewers and EPA personnel who drafted and reviewed these assessments, as well as this Committee (e.g. EPA's Chemical Assessment Advisory Committee (CAAC)), provided no indications to API of subject matter expertise in pathology (on an individual or aggregate basis) equivalent to or exceeding that of professional pathologists that commonly interpret pathological data and that participate on

pathology working groups. API notes that other public commenters had previously requested that expertise in pathology be included[1].

API recognizes that expertise in pathology can be difficult to find and retain. However, a lack of expertise due to resource or logistical issues does not justify conducting these assessments in its absence.

- ***Lack of expert judgement is inconsistent with NRC recommendations***

In the 2014 NRC Review of the EPA's IRIS Process, the NRC recognized the importance of expert judgement and provided specific recommendations for how expert judgement should be recognized and applied[2]:

*"**Recommendation:** More details need to be provided on the recognition and applications of expert judgment throughout the assessment-development process, especially in the later stages of the process. The points at which expert judgment is applied should be identified, those applying the judgment should be listed, and consideration should be given to harmonizing the use of expert judgment at various points in the process."*

Instead of following responsible scientific practice and NRC recommendations, the ETBE and tBA assessments substituted expert judgement in pathology with statistical analysis and EPA science policy[3] to determine human relevance. While statistical analysis and science policy can be valuable tools when appropriately applied, API does not consider them a suitable substitute for scientific expertise in pathology. Inconsistent with the NRC language above, the IRIS assessments for ETBE and tBA fail to clearly describe the points at which expert judgement in pathology was applied or the identities of those applying it. Instead, both assessments justify conclusions based largely on comparison to the relevant EPA science policy. This approach has the potential to result in risk assessments that are defensible and consistent within the context of EPA science policy, yet scientifically indefensible. API contends that this has indeed happened for both the ETBE and tBA assessments for which the human relevance of kidney effects is largely supported by EPA science policy, even though pathological expertise is apparently absent.

- ***Lack of expert judgement is inconsistent with EPA's Peer Review Handbook***

Importantly, the apparent lack of subject matter experts with actual expertise and credentials in (veterinary) pathology is also inconsistent with the description of peer review in EPA's Peer Review Handbook[4]:

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[1] US EPA Science Advisory Board Chemical Assessment Review Committee (CAAC) Augmented for the Review of Ethyl Tertiary Butyl Ether (ETBE) *and* tert-Butyl Alcohol (tBA). Minutes of the Meeting. Public Meeting August 15-17, 2017. Page 12.

[2] Review of EPA's Integrated Risk Information System (IRIS) Process. Committee to Review the IRIS Process, Board on Environmental Studies and Toxicology, Division of Earth and Life Studies, National Research Council of the National Academies. National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001. 2014. ISBN-13: 978-0-309-30414-6. Page 27.

[3] Alpha-2u-globulin: Association with chemically induced renal toxicity and neoplasia in the male rat. EPA/625/3-91/019F. 1991.

[4] US EPA Peer Review Handbook, 4th Edition. Science and Technology Policy Council. October 2015. EPA/100/B-15/001. Page 20.

"It is conducted by qualified individuals (or organizations) who are independent of those who performed the work and who are collectively equivalent in technical expertise to those who performed the original work (i.e., peers)."

API notes that this apparent lack of subject matter expertise in pathology was not without apparent consequence. The meeting Minutes of the 2017 CAAC meeting of ETBE and tBA state[5]:

"Considerable discussion with divergent viewpoints occurred with respect to how the ETBE database for noncancer kidney effects should be interpreted, with no clear consensus reached."

- ***The substantive impact on ETBE and tBA assessments***

The assessments for ETBE and tBA rely heavily upon interpretation of complex and nuanced rodent kidney pathology and assessment of human relevance. It cannot be overstated that the human relevance of these pathological lesions is a crucial point for both assessments that should be informed by expert opinion in pathology in addition to applicable EPA policy. The rationale is that there are few (if any) suitable alternative non-cancer endpoints for the ETBE and tBA assessments. The consequence is that if the kidney effects in rodents for ETBE and tBA were judged to be not relevant to humans, it may not even be possible to conduct a non-cancer risk assessment for ETBE and tBA if suitable alternative endpoints could not be identified.

- ***Expert judgement in pathology should be applied before, during, and after application of EPA science policy to ensure scientific credibility***

An approach for ETBE and tBA that would be consistent with responsible science, NRC recommendations, and EPA science policy would be to first consult expert pathologists for hazard characterization and human relevance. This would ensure that the interpretation of the underlying science is scientifically defensible. The next step would be to have expert pathologists work with experts in applying the relevant EPA science policy to ensure that the resulting product is both scientifically defensible and consistent with EPA science policy. Expert judgement should also be applied after this step to ensure that these risk assessments remain scientifically defensible after they are fed through the mill of the relevant science policy. In the event that applying the relevant EPA science policy results in a scientifically indefensible assessment, the applied science policy should be suspected of generating artefacts and should be revised.

2) Derivations of toxicity values for cancer endpoints for ETBE and tBA were inconsistent with NRC recommendations, EPA guidelines, and the decisions of other EPA Offices. This is a substantive scientific concern because the low dose linear extrapolations applied could result in risks of concern at exposure levels that are orders of magnitude lower than if a threshold (reference dose, aka RfD) approach was used.

- **Derivation of toxicity values was inconsistent with NRC recommendations**

[5] US EPA Science Advisory Board Chemical Assessment Review Committee (CAAC) Augmented for the Review of Ethyl Tertiary Butyl Ether (ETBE) *and* tert-Butyl Alcohol (tBA). Minutes of the Meeting. Public Meeting August 15-17, 2017. Page 6.

In the 2014 NRC Review of the EPA's IRIS Process, the NRC recognized the need for EPA IRIS to determine when toxicity values should be derived[6]:

"Recommendation: *EPA should develop criteria for determining when evidence is sufficient to derive toxicity values. One approach would be to restrict formal dose-response assessments to when a standard descriptor characterizes the level of confidence as medium or high (as in the case of noncancer end points) or as "carcinogenic to humans" or "likely to be carcinogenic to humans for carcinogenic compounds."*

- **Derivation of toxicity values was inconsistent with EPA guidelines/other Offices**

For the 2017 Peer Review Draft for ETBE, EPA's 2005 Guidelines for Carcinogen risk assessment were cited in support of a decision to conduct a dose-response assessment and low-dose linear extrapolation for a selected descriptor of "suggested evidence of carcinogenic potential". This is a lower level of confidence than that suggested in the NRC Recommendation above and is also apparently inconsistent with EPA's 2005 guidelines and the decisions of other EPA offices.

According to EPA's 2005 Guidelines for Carcinogen Risk Assessment[7]:

"When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence."

Although the above language indicates that there may be some situations and purposes for which a dose-response assessment could be warranted for a "suggestive" descriptor, more recent correspondence by other EPA offices (the Office of Pesticide Programs) indicate that, in practice, this is simply not done[8]:

"The classification descriptors "not likely to be carcinogenic to humans" and "suggestive evidence of carcinogenic potential" both utilize a reference dose approach; therefore, a quantitative cancer risk assessment would not be required for either of these descriptors."

- ***The substantive impact on ETBE and tBA assessments***

The impact on toxicity values for a (threshold) reference dose/reference concentration (RfD/RfC) approach versus a dose-response assessment and low-dose linear extrapolation is profound, often impacting risk estimates by orders of magnitude. Depending on the exposure scenario, the difference between a threshold (RfC/RfC) or non-threshold (slope factor, inhalation unit risk

[6] Reference 2 at Page 129.
[7] Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. March 2005. Page 3-2.
[8] Memorandum from G. Akerman and D. Perron to C. Newcamp and N. Anderson. Response to the Final Report of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) on the Evaluation of the Human Carcinogenic Potential of Glyphosate. December 12, 2017. D444688. Page 11.

estimate) approach could be the difference between identifying a risk or concern or being able to provide assurances that an exposure level is orders of magnitude below a safe level.

3) **The numerical value for the oral slope factor for ETBE differs in the Public and Peer Review drafts for ETBE but no rationale was provided. This is not transparent. This is a substantive scientific concern because this value drives the oral cancer risk assessment for this chemical.**

The oral slope factor in the June 2017 IRIS assessment for ETBE is 0.001 mg/kg/day[9], compared to 0.0009 mg/kg/day in the 2016 Assessment[10]. API could find no explanation for the differences in the numerical values.

The substantive impact on ETBE assessments

The (1.1X) difference is slight in magnitude. As such, it is unlikely to substantively impact a risk assessment. The impact is more in the areas credibility and transparency. If values change without reason, then credibility and transparency are damaged.

4) The inconsistencies with NRC recommendations, EPA policy, the practices of other EPA Offices, and the lack of transparency noted above have substantively impacted both assessments. These indicate that recent improvements in the IRIS *process* have yet to result in improved risk assessment *products.* The ETBE and tBA assessments should thus be revised to address these substantive concerns.

API has identified herein scientifically substantive issues that impact the ETBE and tBA risk assessments. Based on the issues and rationale presented above, API maintains that both assessments should be substantially revised. API is well aware that EPA's IRIS *process* is in the midst of wide-spread implementation of change. However impressive these changes in *process* may be, changes in *process* are ultimately irrelevant if they do not result in improved and scientifically defensible risk assessment *products*. It is our hope that our comments will assist the CAAC in advising EPA such that the quality of these IRIS assessments will ultimately be commiserate with the levels of effort that have gone into IRIS reform.

In closing, API appreciates the opportunity to provide comments on the ETBE and tBA assessments to the CAAC.

[9] Toxicological Review of Ethyl Tertiary Butyl Ether. June 2017. EPA/635/R-17/015a.
[10] Toxicological Review of Ethyl Tertiary Butyl Ether. August 2016. EPA/635/R-16/184a.